Approcci interdisciplinari in reumatologia - 7ª edizione

MALATTIE REUMATICHE E DISORDINI ENDOCRINO-METABOLICI

TORINO 16-17 ottobre 2020

Osteoporosi Farmaco-Indotta

Massimo Procopio
SC Endocrinologia, Diabetologia e Metabolismo U
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Collegio Reumatologi Italiani CReI

UNIVERSITÀ DEGLI STUDI DI TORINO

Diseases associated with osteoporosis

Endocrine disorders
Hypogonadism
Hypercortisolism
Hyperparathyroidism
Hyperthyroidism
Hyperprolactinaemia
Diabetes mellitus type 1 and 2
Acromegaly
GH deficiency
Haematologic disorders
Myelo- and lymphoproliferative diseases
Multiple myeloma
Systemic mastocytosis
Thalassemia
Monoclonal gammopathies
Sickle cell anaemia
Haemophilia
Gastrointestinal disorders
Chronic liver disease
Primary biliary cirrhosis
Celiac disease
Chronic inflammatory bowel disease
Gastrointestinal resection
Gastric bypass
Lactose intolerance
Intestinal malabsorption
Pancreatic insufficiency
Rheumatic disorders
Rheumatoid arthritis
Systemic lupus erythematosus
Ankylosing spondylitis
Psoriatic arthritis
Scleroderma
Other connective tissue diseases

Kidney diseases
Idiopathic renal hypercalciuria
Renal tubular acidosis
Chronic kidney disease
Neurologic disorders
Parkinson's disease
Multiple sclerosis
Paraplegia
Sequelae of stroke
Muscular dystrophies
Genetic disorders
Osteogenesis Imperfecta
Ehlers-Danlos
Gaucher's disease
Glycogenosis
Hypophosphatasia
Haemochromatosis
Homocystinuria
Cystic fibrosis
Marfan syndrome
Menkes syndrome
Porphyria
Riley-Day syndrome
Other disorders
Chronic obstructive pulmonary disease
Anorexia nervosa
AIDS/HIV
Amyloidosis
Sarcoidosis
Depression

Linee Guida SIOMMMS 2016

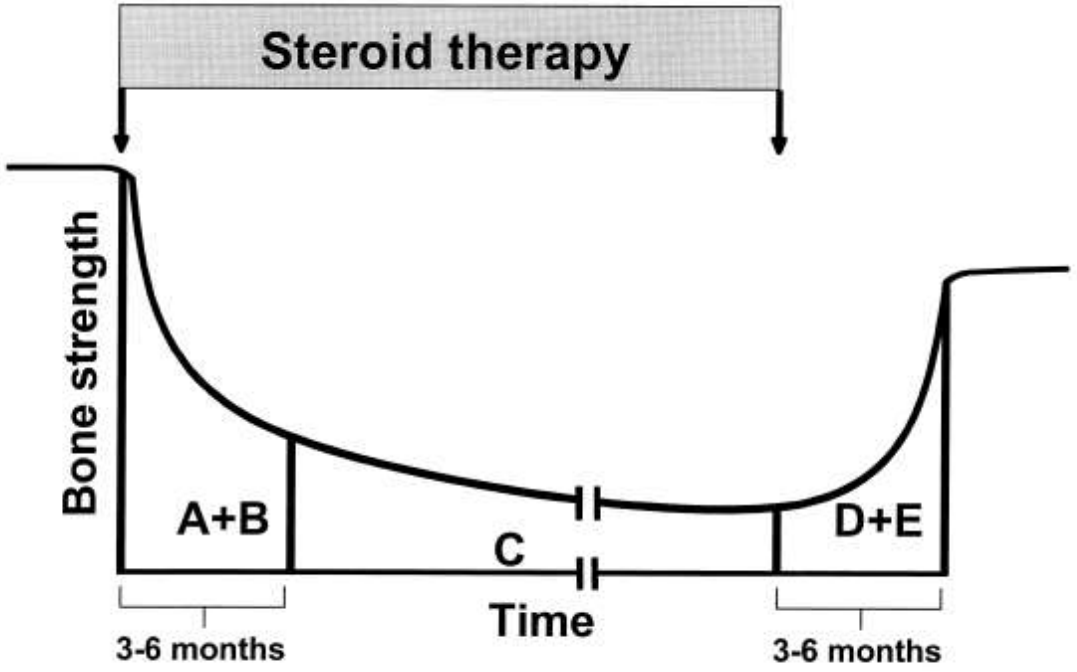
Drugs associated with bone loss

Drug class	Active substance	Possible mechanism of action
Glucocorticoids*	Hydrocortisone, prednisone, dexamethasone	Inhibition of osteoblast activity/osteocyte apoptosis
Aromatase inhibitors*	Letrozole, anastrozole, examestane	Hypogonadism with high turnover
SSRIss*	Citalopram, fluoxetine, paroxetine	Inhibition of osteoblast proliferation, RANKL activation
Proton pump inhibitors*	Esomeprazole, omeprazole, lansoprazole	Reduced calcium intestinal absorption
H2-inhibitors	Ranitidine, cimetidine	Reduced calcium absorption
Thiazolidinediones*	Rosiglitazone, pioglitazone	Inhibition of bone formation and osteoblast differentiation
Thyroid hormone (excess)*	Levothyroxine	Increased bone turnover
Anticoagulants*	Heparin, warfarin	Reduced osteocalcin activity
Anticonvulsants*	Phenobarbital, valproic acid, oxcarbazepine, phenytoin	Altered vitamin D metabolism
GnRH*	Leuprolide, goserelin	Hypogonadism with high turnover
Loop diuretics	Furosemide	Calciuric effect
Antiretroviral agents	Efavirenz, nevirapine Tenofovir Protease inhibitors	Altered vitamin D metabolism Increased urinary phosphate excretion Inhibition of osteoblastogenesis/increased RANKL
Calcineurin inhibitors*	Ciclosporin A (high doses), tacrolimus	Increased bone turnover. Increased RANKL expression
Parenteral nutrition		Unclear

*Evidence for an association with fracture risk. SSRI, selective serotonin reuptake inhibitors; GnRH, gonadotropin-releasing hormones.

Linee Guida SIOMMMS 2016

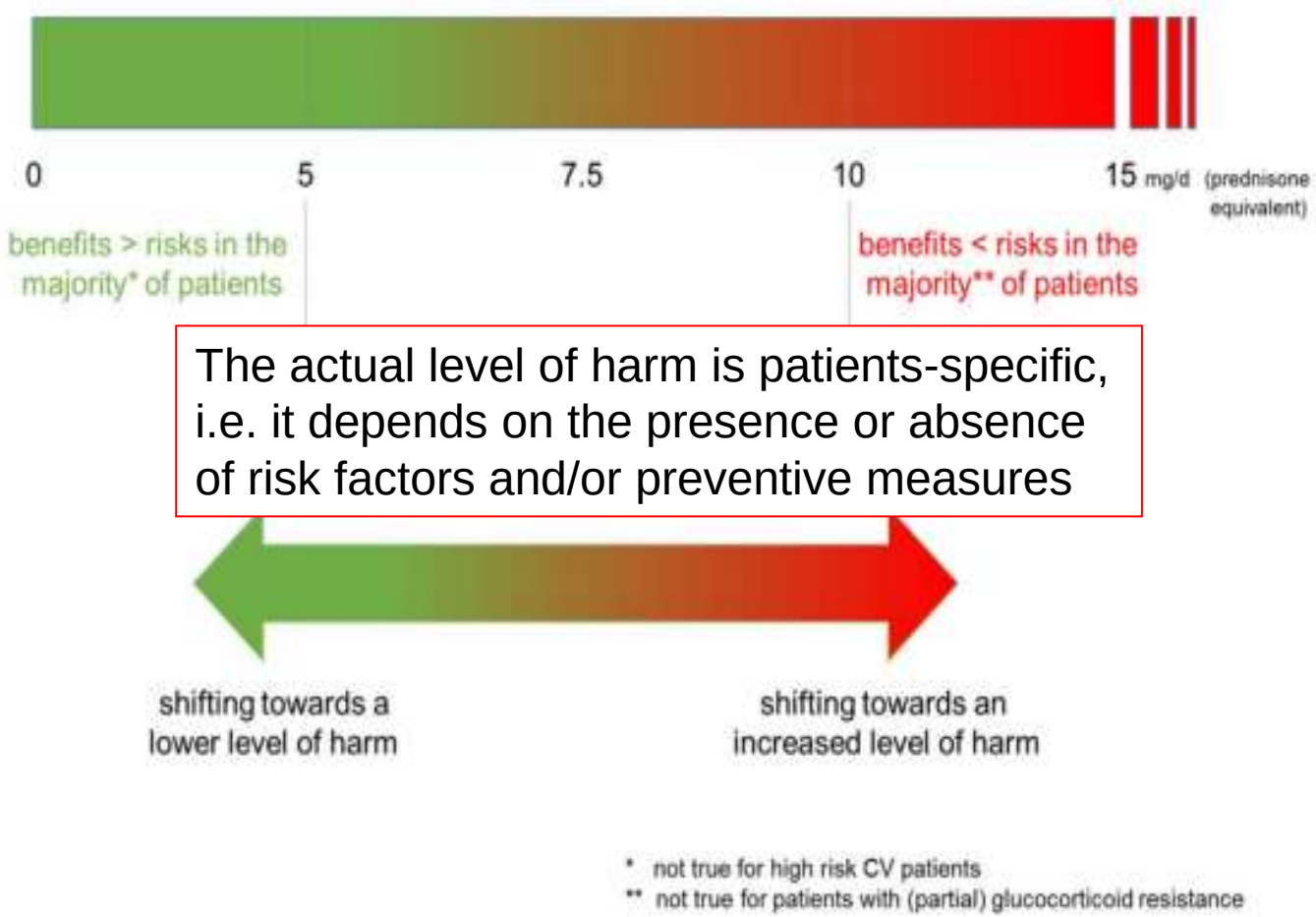
Rapid Onset and Offset of Fracture Risk with Glucocorticoid Treatment



A= osteocyte apoptosis leading to deterioration of bone quality
B= fast bone loss due to a "relative" increase in resorption without corresponding formation in pre-existing BMUs
C= gradual accumulation of unrepaired defects due to suppressed remodeling
D= fast repair of defects by resurgent remodeling
E= restoration of osteocyte network leading to improved bone quality

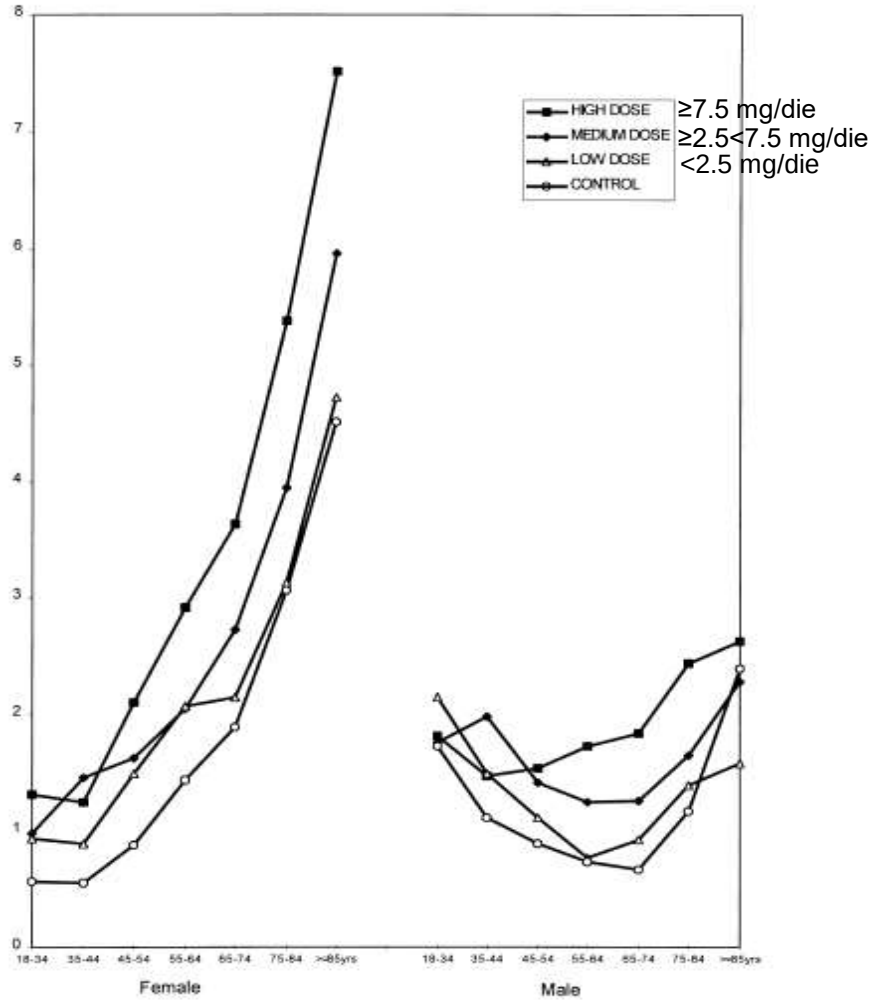
Terapia Cortisonica nelle Malattie Reumatiche

Level of Harm of Long-term Glucocorticoid Therapy in Rheumatic Diseases



Strehl C et al. Ann Rheum Dis 75:952–957, 2016

Incidence of nonvertebral fractures stratified by daily corticosteroid dose, age, and gender.



Van Staa TP et al. Journal Of Bone And Mineral Research15, 993-1000, 2000

Prevalence and incidence of osteoporotic fractures in patients on long-term glucocorticoid treatment for rheumatic diseases: the Glucocorticoid Induced OsTeoporosis TOol (GIOTTO) study

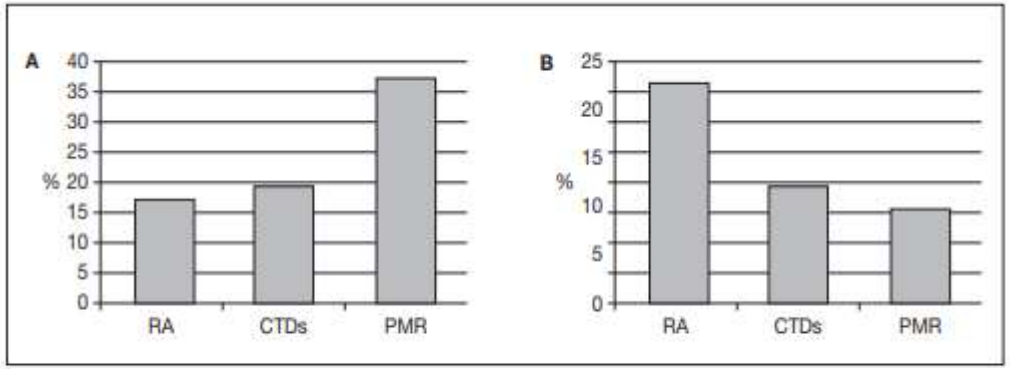


Figure 2 - A) Prevalence of patients with fractures pre-GC treatment, according to the Rheumatic Diseases; B) Prevalence of patients with new clinical fragility fractures in the different Rheumatic Diseases during GC treatment.

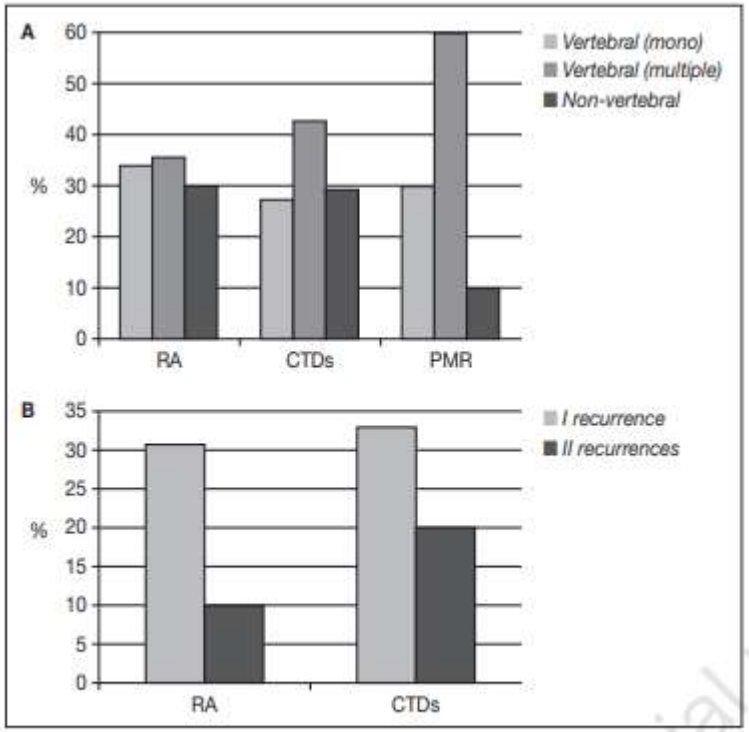
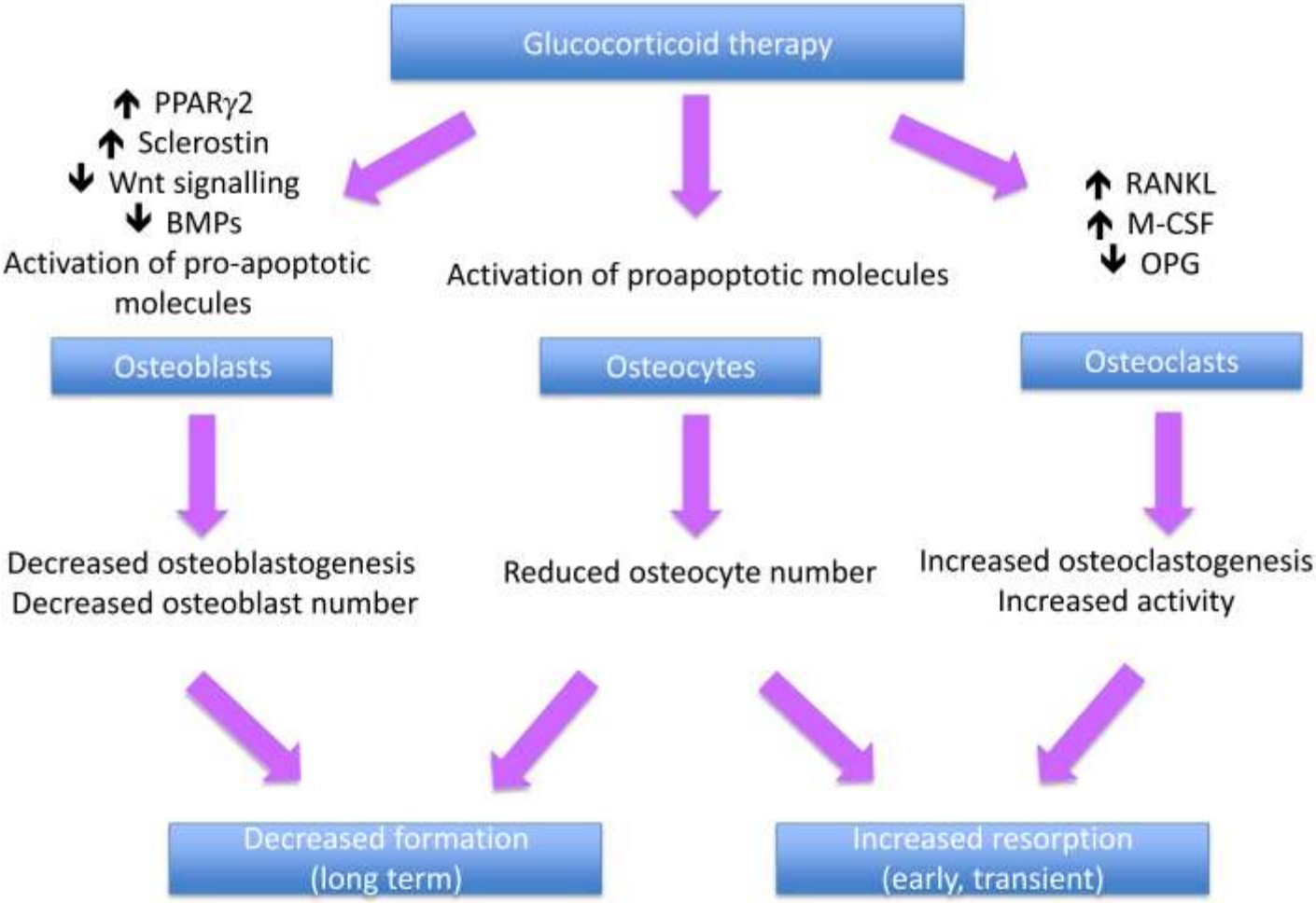


Figure 3 - A) Distribution of different types of fractures, in the different diseases, during GC treatment; B) Prevalence of RA or CTDs patients with recurrence of fractures during GC treatment.

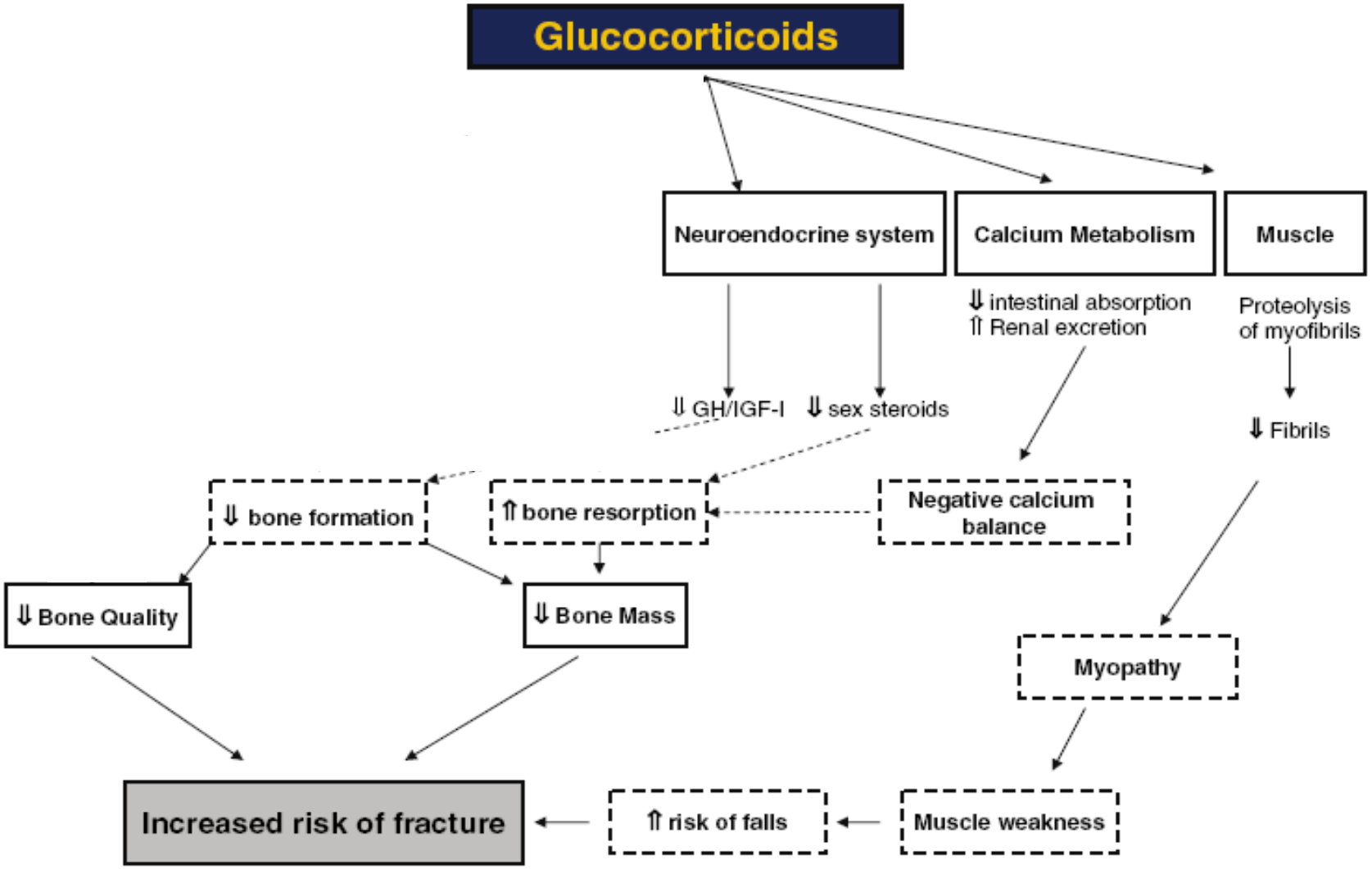
Rossini M et al. Reumatismo 69: 30-39, 2017

Direct Effects of Glucocorticoids on Bone

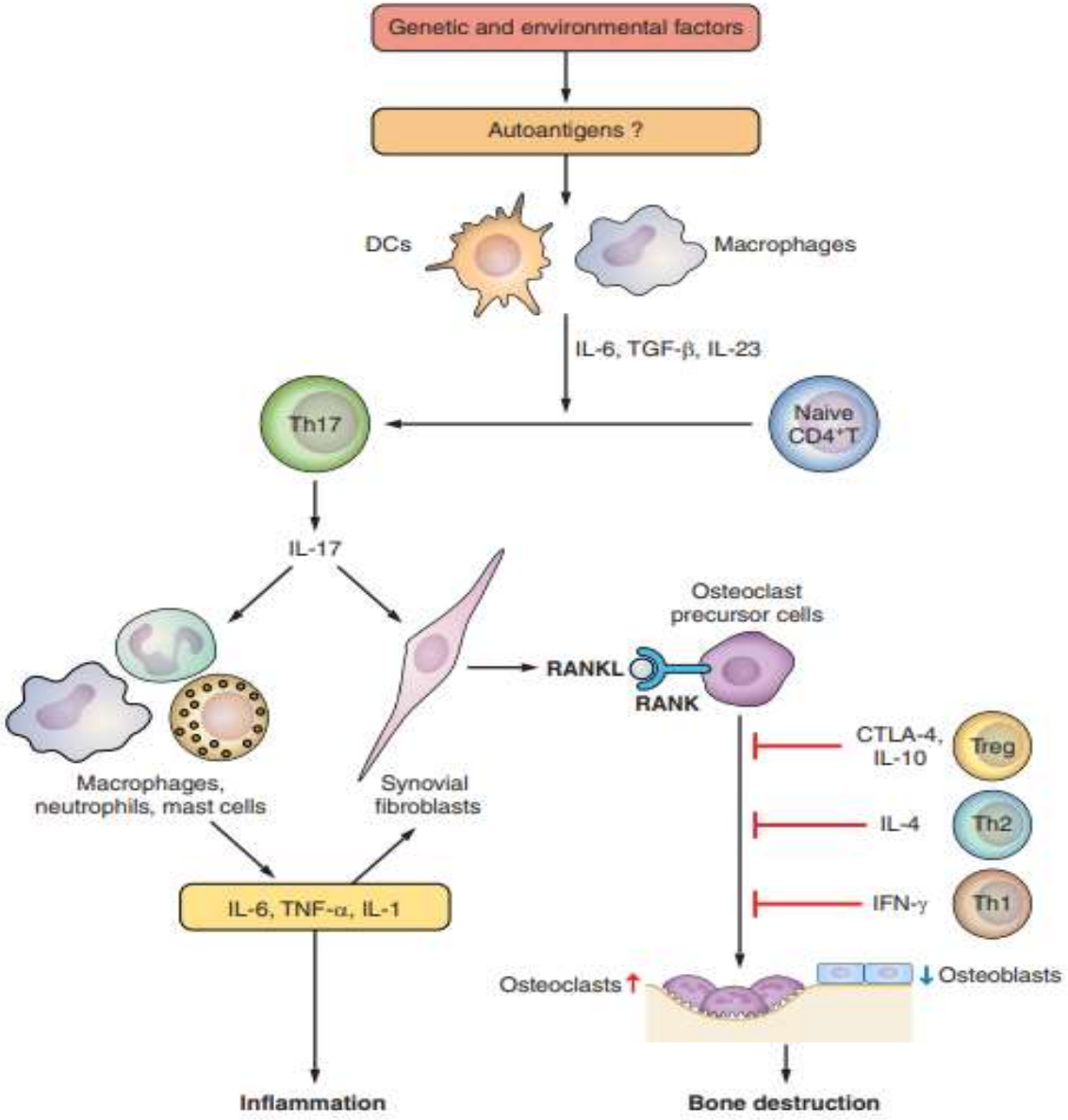


Compston J, Endocrine 61:7-16,2018

Direct and Indirect Effects of Glucocorticoids on Bone

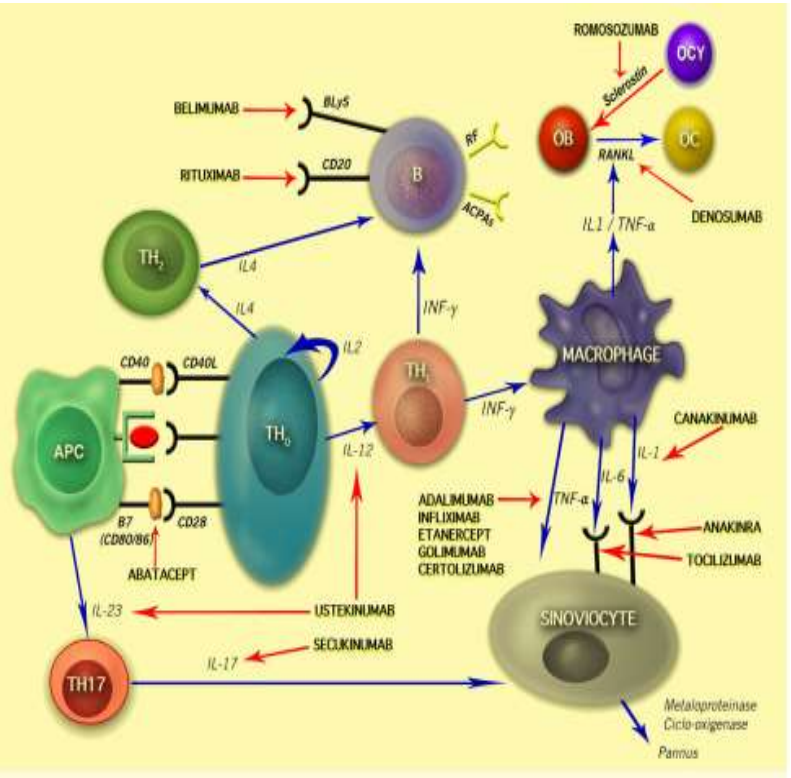


Bone Destruction in Rheumatoid Arthritis



Okamoto K et al. Physiol Rev 97: 1295–1349, 2017

The effect of biologic agents on bone homeostasis in chronic inflammatory rheumatic diseases



Zerbini CAF et al. Osteoporos Int 28:429-446, 2017

Key messages

• ….**inflammation plays a harmful role on both local and systemic bone loss**, which may ultimately lead to disability and mortality. **Early and powerful inhibition of inflammation is paramount in counteracting local and systemic bony damage**.

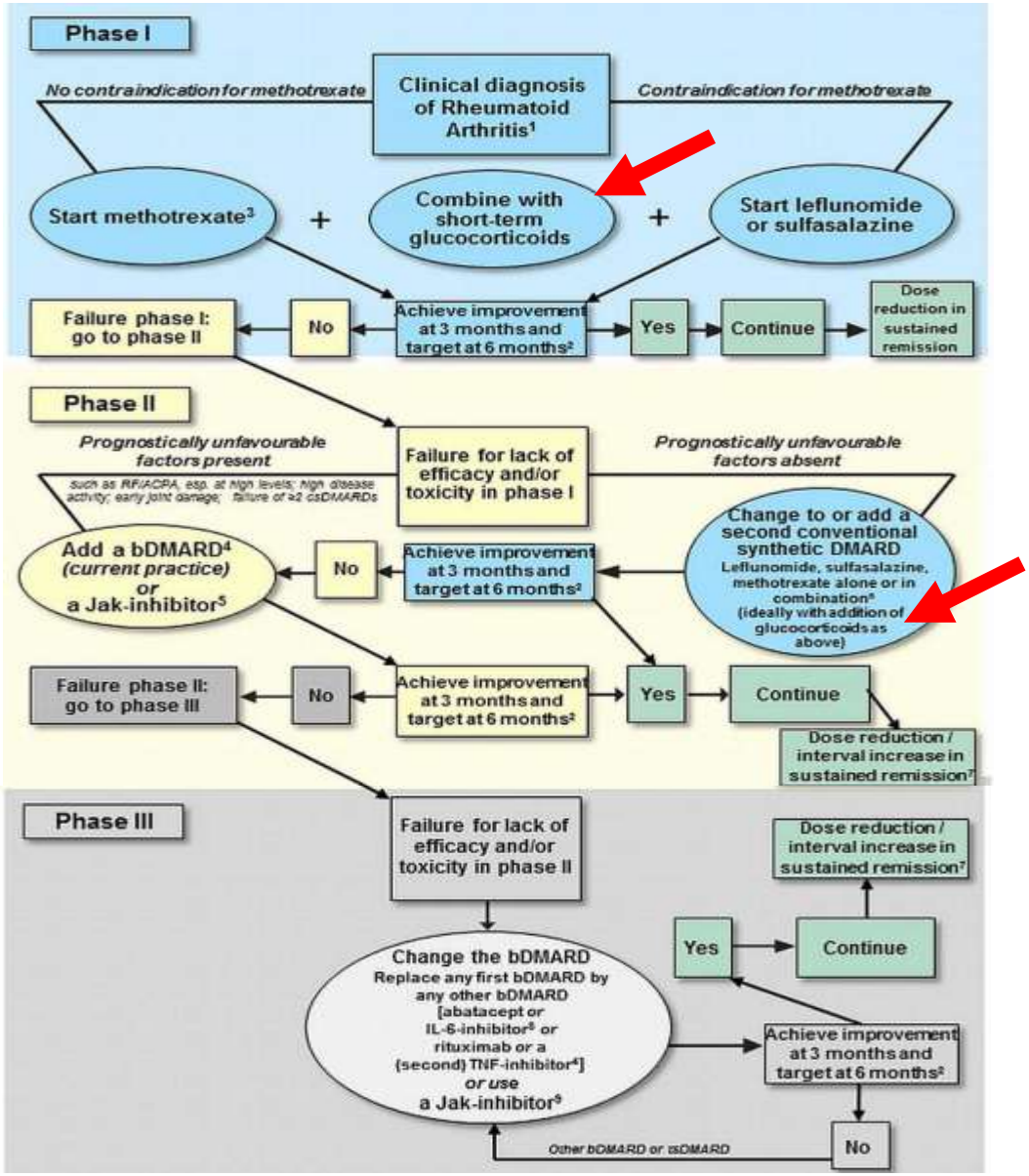
• Biologic agents **have proved to positively influence disrupted bone homeostasis** documented in all CIRDs by interfering with BTs and systemic bone loss. However, if these effects can also translate into **reduced fracture risk remains to be determined**.

• Whether the co-administration of biologic agents with DNB, the monoclonal antibody against RANKL successfully used in systemic OP, could offer a better outcome in preserving BMD and possibly reduce fracture risk, is not fully investigated.

• Rheumatologists should improve their awareness, so far largely suboptimal, of the need for screening, and prevention, or proper treatment of systemic bone loss and increased fracture rates also in patients placed on biologics.

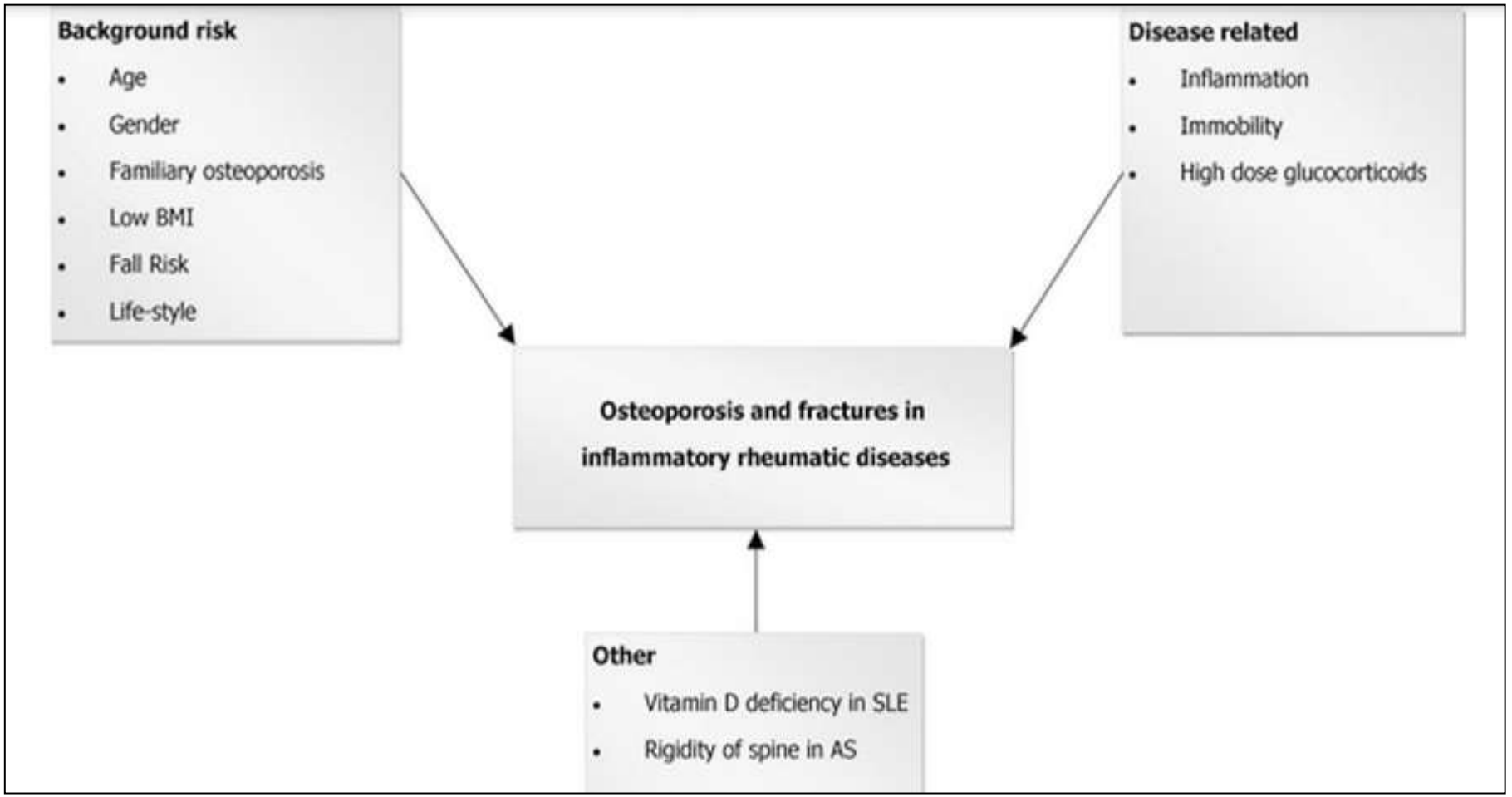
Di Munno O & Ferro F Clin Exp Rheumatol 37: 502-507, 2019

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update



Smolen JS et al. Ann Rheum Dis 2017;76:960–977.

Risk Factors for Osteoporosis and Fractures in Inflammatory Rheumatic Diseases



Zerbini CAF et al. Osteoporos Int 28:429-446, 2017

DXA = Gold Standard

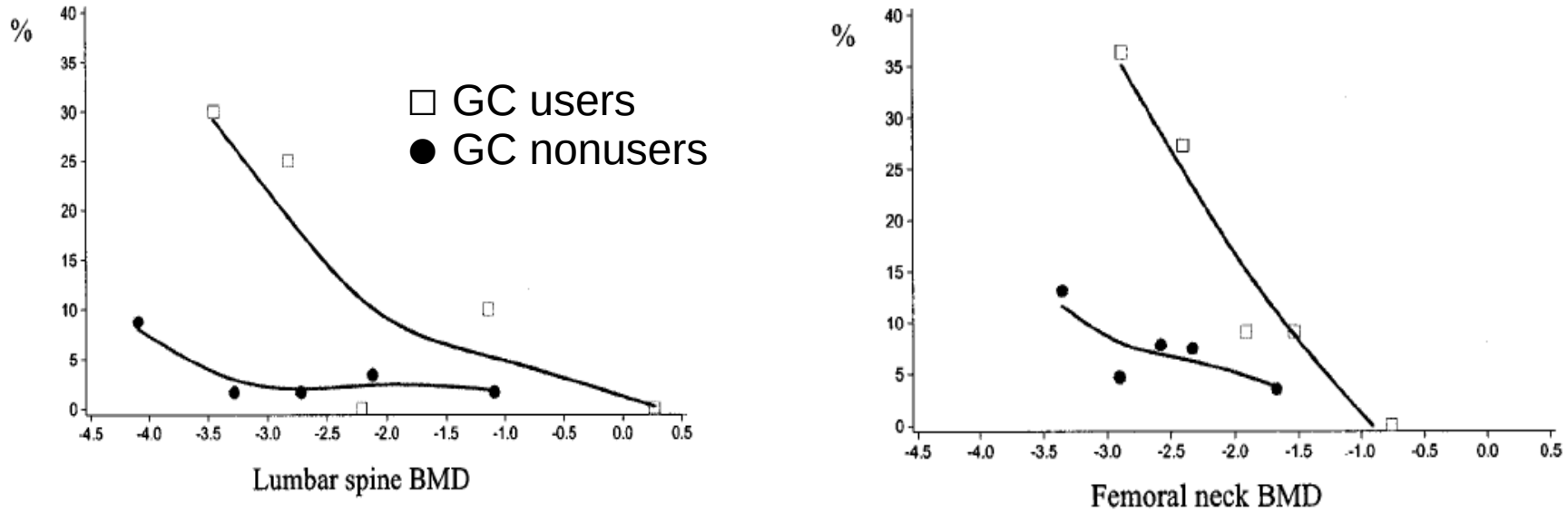
Definizioni diagnostiche in T-score nelle donne in post-menopausa e negli uomini di età >50 aa, secondo la WHO.

T-score	Diagnosi
≥ -1	NORMALE
da -1 a –2.5	OSTEOPENIA
≤ -2.5	OSTEOPOROSI
≤ -2.5 con frattura osteoporotica	OSTEOPOROSI CONCLAMATA o SEVERA

Definizioni diagnostiche in Z-score nelle donne in pre-menopausa o nei maschi di età inferiore a 50 anni .

Z-score	Diagnosi
≥+2	Superiore al range atteso per età
da -2 a +2	Nel range atteso per età
≤ -2.0	Inferiore al range atteso per età

Incidence of vertebral fracture in patients receiving glucocorticoids (GCs) compared with nonusers of GCs, by baseline lumbar spine bone mineral density (BMD) and femoral neck BMD.



The individual data points correspond to the incidence in subgroups of the GC user and nonuser populations, as based on quintiles of baseline BMD. The solid line is a curve representing smoothing of these individual estimates.

Van Staa TP et al. Arthritis & Rheumatism 48:3224–3229, 2003

Indications for vertebral fracture testing

Conventional spine x-ray or VFA are indicated:

- in the presence of symptoms suggestive for vertebral fracture: intense back pain that worsens with standing, current or past

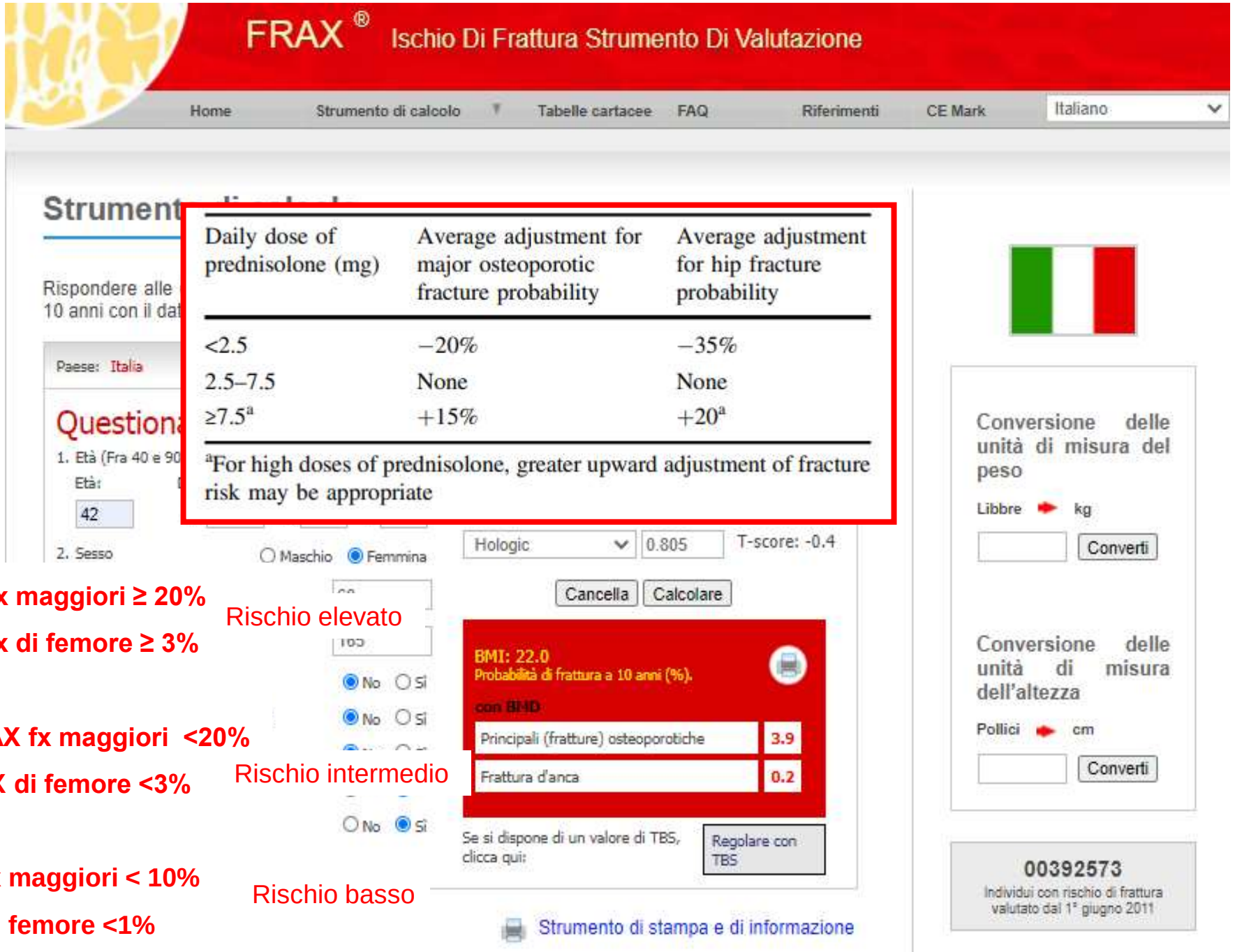
- in the absence of symptoms:

i) in all women aged >70 years and men aged >80 years;

ii) in all women aged between 65 and 69 years and in men aged between 70 and 79 years, if T-score <-1.5;

iii) in postmenopausal women and men aged 50 years or older with specific risk factor:

- Previous fragility fractures
- A height loss >4 cm in comparison with young age or >2 cm from the last visit
- Marked reduction in densitometric values (T-score <-3)
- Glucocorticoid therapy with prednisone >5 mg per day or equivalent for>3 months
- Comorbidities associated with an increased risk of vertebral fractures per se.



FRAX fx maggiori ≥ 20%

FRAX fx di femore ≥ 3%

Rischio elevato

≤10 FRAX fx maggiori <20%

≤1 FRAX di femore <3%

Rischio intermedio

FRAX fx maggiori < 10%

FRAX di femore <1%

Rischio basso

https://www.sheffield.ac.uk/FRAX/tool.aspx?lang=it

DEFRA®
L'ALGORITMO PER LA STIMA DEL RISCHIO DI FRATTURA

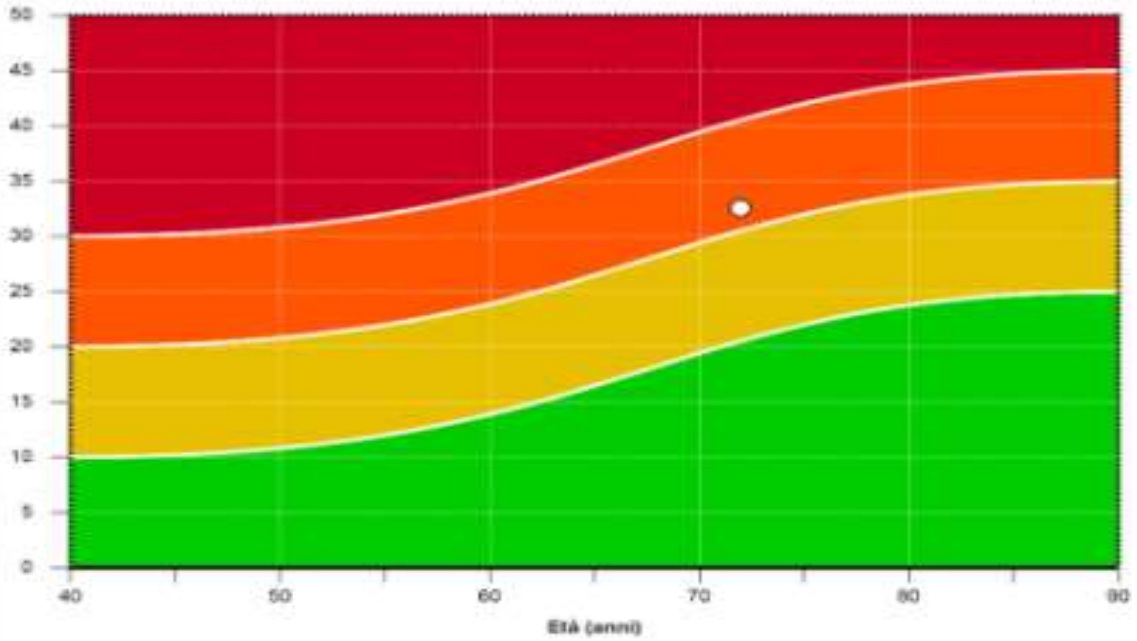
Benvenuto massimo procopio

PROFILO LOGOUT ?

NUOVO CALCOLO | STATISTICHE | IMPOSTAZIONI | L'ALGORITMO | DEFRACALC | SUPPORTO E ASSISTENZA

HOME / MASSIMO PROCOPIO: NOTA 79

Carta del rischio DeFRACALC NOTA79



Eligibile nota 79: Si
Rischio di fratture maggiori a 10 anni: 33%

Farmaci I linea: alendronato, risedronato, zoledronato
Farmaci II linea: denosumab
Note: La prescrizione va fatta nel rispetto delle indicazioni e avvertenze della nota 79 e della scheda tecnica dei singoli farmaci

DATA VISITA:	10/10/2020 11:30
CODICE VISITA/PAZIENTE:	
ETÀ:	72
SESSO:	F menopausa
PESO:	60 Kg
ALTEZZA:	165 cm
STORIA FAMILIARE FRATTURA FEMORE E VERTEBRE:	No
PREGRESSE FRATTURE VERTEBRALI O DI FEMORE:	No
ALTRE PREGRESSE FRATTURE OSTEOPOROTICHE:	No
FARMACI CHE AUMENTANO IL RISCHIO DI FRATTURA:	Cortisonici >3mesi
COMORBILITÀ CHE AUMENTANO IL RISCHIO DI FRATTURA:	Artrite reumatoide
TSCORE FEMORE:	-0,40
TSCORE COLONNA:	-1,50

Terapia prescritta*

(seleziona una risposta)

Esami di laboratorio

Primo livello

- ✓ VES
- ✓ Emocromo completo
- ✓ Quadro proteico elettroforetico
- ✓ Calcemia totale
- ✓ Fosforemia
- ✓ Fosfatasi alcalina totale
- ✓ Creatininemia
- ✓ Calciuria 24 ore

Secondo livello

- ✓ Calcio ionizzato
- ✓ TSH
- ✓ PTH
- ✓ 25 OH-Vitamina D sierica
- ✓ Cortisoluria 24 ore
- ✓ Testosterone totale nei maschi
- ✓ Immunofissazione sierica e/o urinaria
- ✓ Screening celiachia
- ✓ Esami specifici per patologie associate

Terapia non farmacologica

- Dose minima efficace del farmaco cortisonico
- Prevenzione delle cadute
- Esercizio fisico regolare
- Evitare fumo ed abuso alcolico
- Apporto di calcio adeguato
- Vitamina D

Nota 96

*La prescrizione a carico del SSN dei farmaci con indicazione "**prevenzione e trattamento della carenza di vitamina D**" nell'adulto (>18 anni) è limitata alle seguenti condizioni:*

Prevenzione e trattamento della carenza di vitamina D nei seguenti scenari clinici :

Farmaci inclusi nella Nota AIFA:
- colecalciferolo
- colecalciferolo/Sali di calcio
- calcifediolo

indipendentemente dalla determinazione della 25(OH) D

- persone istituzionalizzate
- donne in gravidanza o in allattamento
- persone affette da osteoporosi da qualsiasi causa o osteopatie accertate non candidate a terapia remineralizzante (vedi nota 79)

Nota 96

*La prescrizione a carico del SSN dei farmaci con indicazione "**prevenzione e trattamento della carenza di vitamina D**" nell'adulto (>18 anni) è limitata alle seguenti condizioni:*

Prevenzione e trattamento della carenza di vitamina D nei seguenti scenari clinici :

previa determinazione della 25(OH) D (vedi algoritmo allegato)

- persone con livelli sierici di 25OHD < 20 ng/mL e sintomi attribuibili a ipovitaminosi (astenia, mialgie, dolori diffusi o localizzati, frequenti cadute immotivate)
- persone con diagnosi di iperparatiroidismo secondario a ipovitaminosi D
- persone affette da osteoporosi di qualsiasi causa o osteopatie accertate candidate a terapia remineralizzante per le quali la correzione dell'ipovitaminosi dovrebbe essere propedeutica all'inizio della terapia *
- una terapia di lunga durata con farmaci interferenti col metabolismo della vitamina D
- malattie che possono causare malassorbimento nell'adulto

Farmaci inclusi nella Nota AIFA:

- colecalciferolo
- colecalciferolo/Sali di calcio
- calcifediolo

Level of Evidence of Pharmacological Therapy for Glucocorticoid-induced Osteoporosis

Pharmacological intervention	Treatment target			
	BMD	Vert Fx	Non-vert. Fx	Hip Fx
Alendronate	1	1*	-	-
Risedronate	1	1*°	-	-
Clodronate	1#	2#	-	-
Teriparatide	1	1	-	-
Zoledronate	1§	-	-	-
Denosumab	2#	-	-	-

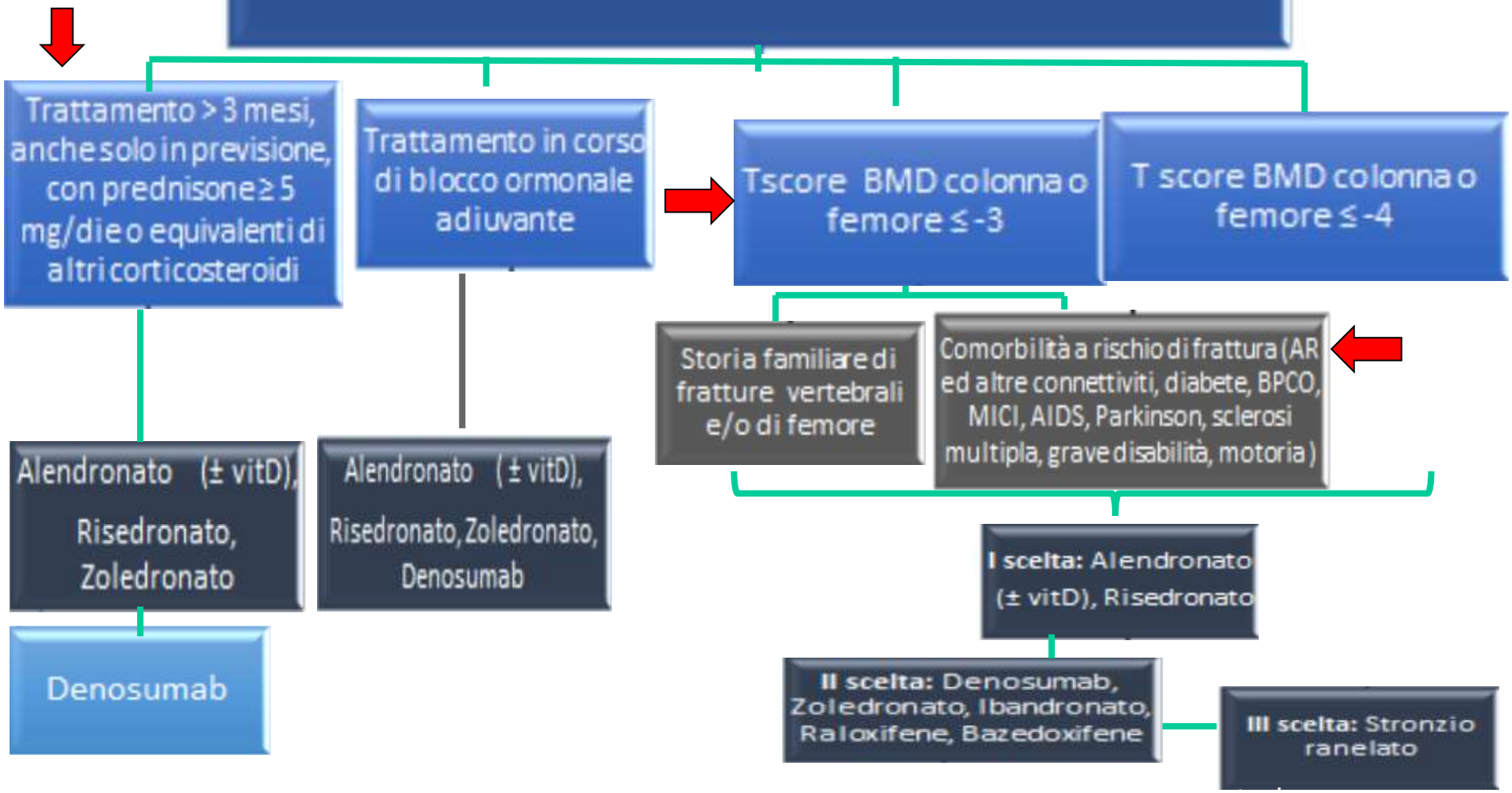
BMD, bone mineral density. *Non primary end-point; °from a meta-analysis of 2 trials; #randomized, open label, single centre study, using 100 mg i.m. per week; no specific therapeutic indication in the Summary of Product Characteristics; §greater densitometric increases compared to risedronate in a head-to-head study.

Level of evidence	Criteria
1	Systematic overview of meta-analysis of randomised controlled trials
2	Randomised controlled trial that does not meet Level 1 criteria
3	Non-randomised controlled trial or cohort study

Linee Guida SIOMMMS 2016

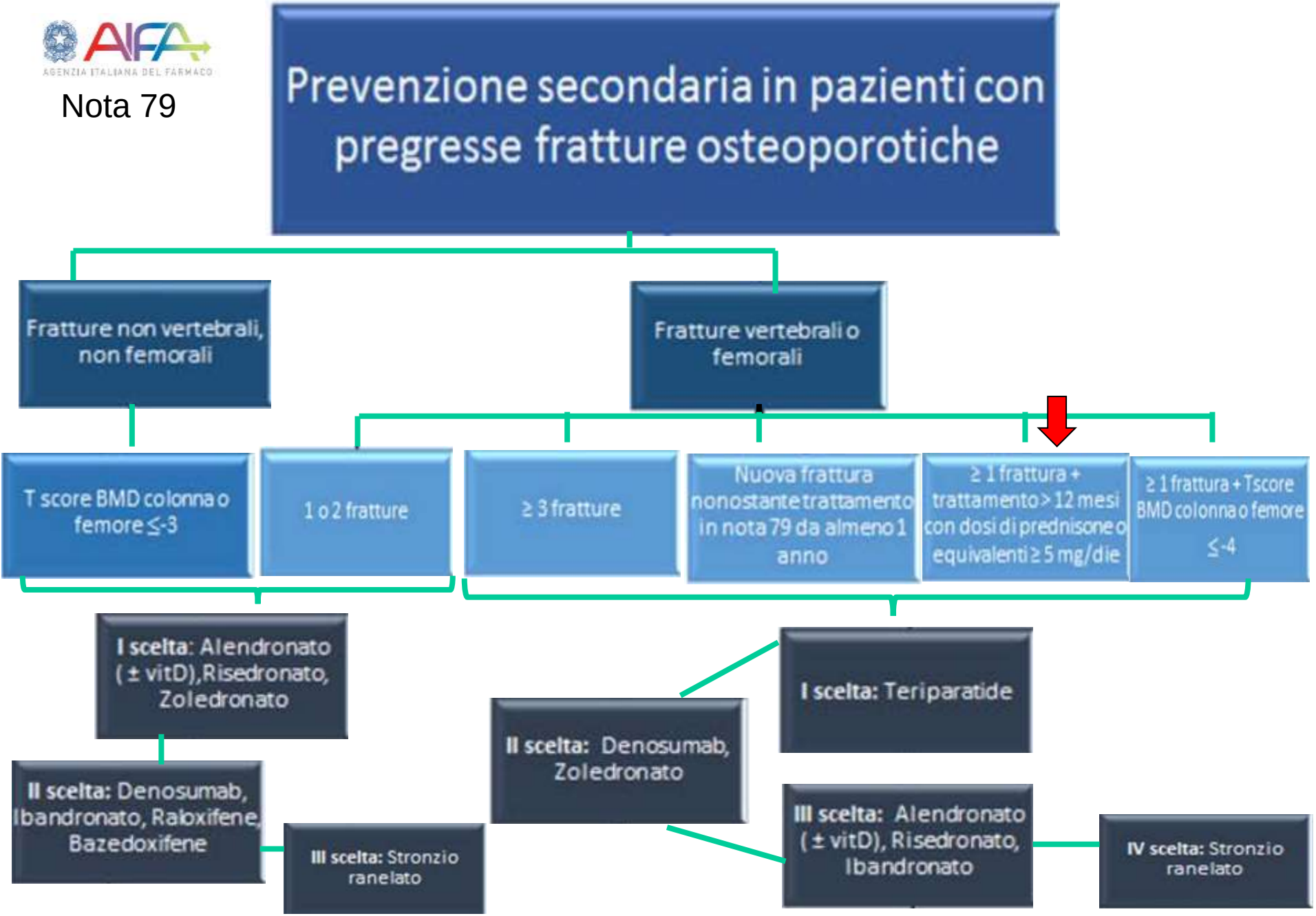
NOTA 79

Prevenzione primaria in donne in menopausa o maschi ≥50 anni con rischio di frattura elevato

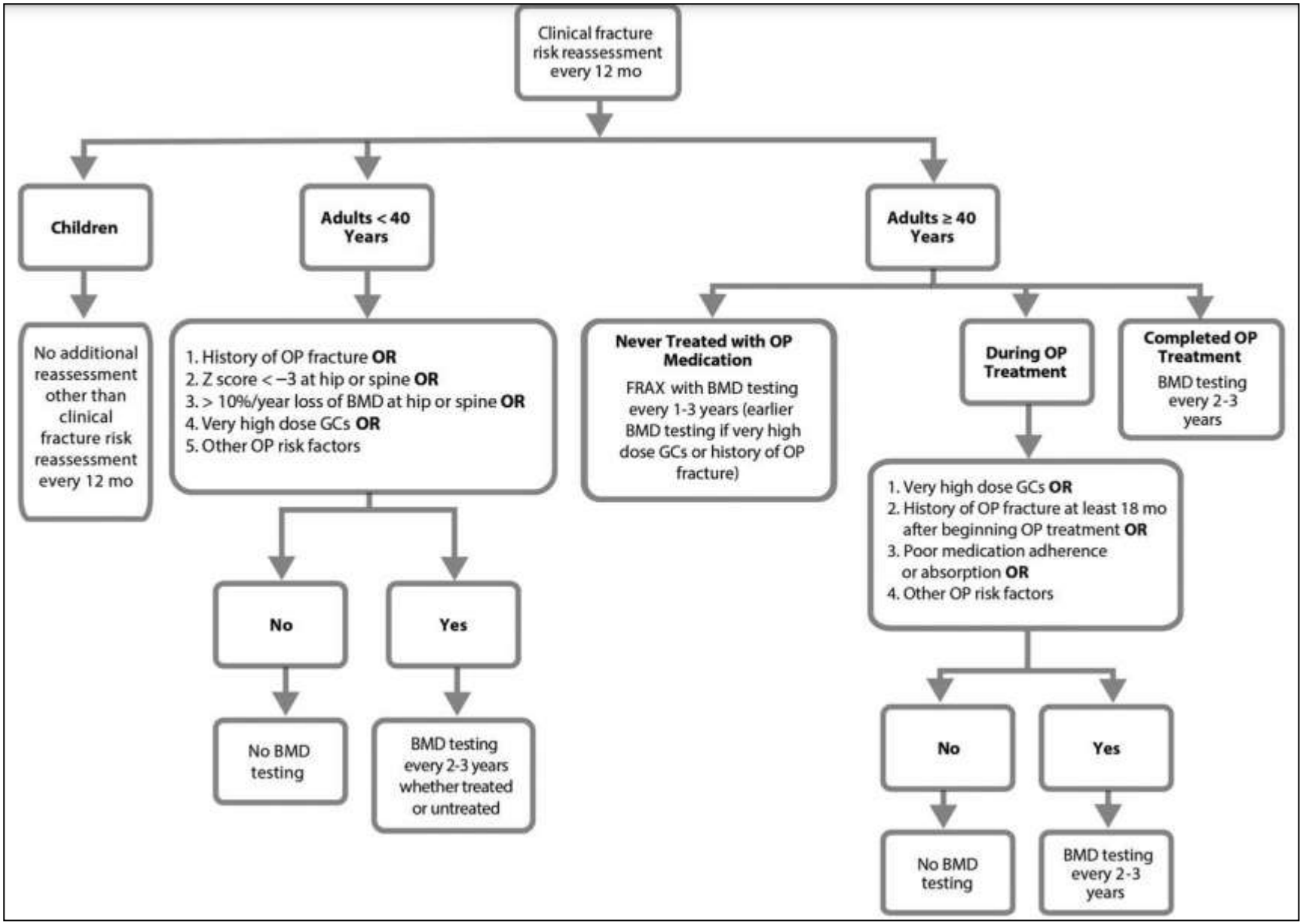


Nota 79

Prevenzione secondaria in pazienti con pregresse fratture osteoporotiche



Reassessment of fracture risk



Buckley L et al. Arthritis Care & Research 69:1095–1110, 2017

Conclusioni

Nelle malattie reumatiche:

- l'osteoporosi indotta da glucocorticoidi è ancora sottodiagnosticata e sottotrattata
- i glucocorticoidi possono e debbono essere utilizzati in modo appropriato (dose minima efficace)
- i pazienti devono essere valutati dal punto di vista del rischio fratturativo mediante appositi algoritmi
- dopo esclusione di cause contributive di malattia devono essere messi in atto misure terapeutiche generali (adeguato apporto di calcio e vitamina D) e trattamenti antifratturativi specifici con farmaci antirassorbitivi (bisfosfonati, Dmab) od anabolici (teriparatide)


GRAZIE DELL'ATTENZIONE